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Preventing the Conversion from Prediabetes to Type 2 Diabetes Mellitus: Lifestyle Modification versus Metformin Therapy

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By

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CASE

A 42-year-old mildly obese female returns to her primary care provider for lab results. Her screening comprehensive metabolic panel reveals an impaired fasting glucose of 120 mg/dL and her glycosylated hemoglobin A1c (HbA1c) is 6.3 – squarely in the prediabetic range, bordering on conversion to type 2 diabetes mellitus (T2DM). At this point, should the clinician recommend lifestyle modifications alone? Lifestyle modifications and metformin? Would those recommendations necessarily vary if she was 65 years old or had a history of gestational diabetes (GDM)?

INTRODUCTION

The aforementioned clinical scenario is commonplace in medical offices worldwide. Prediabetes, generally accepted as an impaired fasting glucose (IFG) with a fasting blood glucose level of 100 to 125 mg/dL, a HbA1c of 5.7% to 6.4%, or an impaired oral glucose tolerance (IGT) with a plasma glucose of 140 to 199 mg/dL 2 hours after a 75g glucose load, affects nearly one-third of American adults, or 84 million individuals.[1,2,3] Among those 65 years or older, the incidence of prediabetes rises to nearly 50%.[4] In those with newly acquired IFG, the natural disease course can result in T2DM in one-third of patients within just 2.5 to 3 years.[5] The rate of cumulative T2DM incidence may be as high as 65% by 6 years among those with both IFG and IGT, in contrast with just 5% among those with normal baseline glucose levels (i.e. a fourteen-fold increase in relative risk).[6]

Overt diabetes is both economically and physiologically costly. Average medical expenditures among diabetics are over double those of non-diabetics, with cardiovascular complications contributing the most to overall costs.[7] Moreover, diabetes is associated with a myriad of micro- and macrovascular complications, such as nephropathy, retinopathy, and atherosclerotic cardiovascular disease (CVD). Compared to persons with normoglycemia, diabetics have twice the risk of all-cause mortality.[8] Indeed, diabetes was the seventh leading cause of death in the United States in 2017 and is listed as the primary cause of death in over 1.3 million Americans annually.[9]

Epidemiological and interventional studies suggest that prediabetes is also not benign; the risks and adverse consequences begin early in the progression from normoglycemia to diabetes. For instance, characteristically diabetic retinopathy has been observed in approximately 8% of the prediabetic population and the prevalence nearly doubles with the onset of T2DM.[10] Recent evidence is conflicting as to whether prediabetes represents an independent CVD risk factor, as the increased incidence of CVD events and mortality in this population may stem from concurrent cardiometabolic risk factors.[8,11] Still, CVD mortality rates among those with prediabetes by HbA1c are approximately 15% higher than among those with normoglycemia.[10] Data also suggest a linear relationship between CVD risk and glycemic indices, even within the prediabetic range.[8] It is possible that although prediabetes may not represent an independent CVD risk factor, it may function as an ancillary risk factor in the setting of other cardiovascular comorbidities, such as dyslipidemia, hypertension, or tobacco use. This associated risk underscores the importance of addressing all cardiovascular risk factors in the setting of hyperglycemia.

The brief potential window for conversion to T2DM, given its inherent dangers and detriments, places the medical provider in a pivotal position to prevent or delay the onset of T2DM once prediabetes is identified. The American Diabetes Association (ADA)'s recommendations regarding prediabetes largely result from the seminal Diabetes Prevention Program (DPP) study. In its *Standards of Medical Care in Diabetes 2019*, the ADA recommends intensive behavioral modifications for all patients.[1] Furthermore, for prediabetics considered at highest risk (i.e. BMI ≥ 35 kg/m^2, less than 60 years of age, or prior gestational diabetes), the ADA recommends, with the highest level of evidence rating, adding pharmacological therapy with metformin; the ADA cites that metformin has the strongest evidence base and demonstrated long-term safety as pharmacologic therapy for diabetes prevention.

Despite the inclusion of metformin into the preventative algorithm in 2008, however, a large retrospective cohort analysis of over 17,000 individuals with prediabetes found that only 3.7% were prescribed the medication over a multi-year study window.[12] Furthermore, the prescription rate was less than 8% among those at highest risk for conversion to T2DM per ADA guidelines. Whether due to knowledge gaps or a preference for non-pharmacological management, this finding underscores a lack of clinical implementation of evidence-based guidelines. More importantly, this observation reveals a potentially significant missed opportunity to delay or prevent the development of an epidemic and often fatal disease. The purpose of this paper is to examine the evidence regarding the roles and efficacy of lifestyle modifications and metformin in the prevention or delay of T2DM in prediabetic individuals. The relative safety, tolerability, and cost-effectiveness of the interventions are addressed elsewhere and are not discussed in the present analysis.

DISCUSSION

One pivotal double-blinded randomized controlled trial (RCT) tested the performance of intensive behavioral modifications versus metformin on the incidence of new-onset T2DM in overweight and obese prediabetic adults.[13] The DPP study involved over 3,000 individuals across the United States. Participants were randomized to receive either intensive lifestyle intervention, metformin, or placebo, and then they were monitored periodically for the development of diabetes. Those in the lifestyle arm were assisted with improving dietary choices, reducing overall caloric intake, increasing moderate-intensity physical activity (≥150 minutes per week), and achieving a weight loss goal of 7% of initial body weight. The metformin group participants were titrated up to 850 mg twice daily. After a mean follow-up of approximately 3 years and a medication washout period, the lifestyle intervention group and the metformin group had respective T2DM incidences of 58% and 25% lower than controls.[14] Comparing the lifestyle and metformin groups directly, the lifestyle cohort had nearly 40% fewer cases of new-onset T2DM. These results were observed in the context of suboptimal lifestyle adherence, with approximately 40% failing to achieve activity goals; whether these goal-attainment levels are widely generalizable is unknown. Interestingly, metformin was most effective at higher baseline BMIs and fasting glucose levels, while lifestyle interventions were more protective in older individuals.

A prospective analysis of additional metabolic factors among the DPP cohorts demonstrated that lifestyle modifications, but not metformin therapy, improved several

Framingham CVD risk factors during the active intervention period.[15] While the prevalence of hypertension and hyperlipidemia increased in the metformin and placebo arms despite greater utilization of medication management, the lifestyle cohort saw improved systolic and diastolic blood pressures, decreased atherogenic low-density lipoprotein (LDL) particles, as well as increased high-density lipoprotein (HDL) particle levels.

The Diabetes Prevention Program Outcomes Study (DPPOS) sought to investigate the original DPP inquiries at 10 years post-randomization.[16] The metformin cohort underwent an open-label extension while lifestyle interventions were reinforced in the original lifestyle group. While the intergroup differences in incident T2DM declined over time, the cumulative T2DM incidence remained significantly lower in the lifestyle group versus the metformin group. It is important to note, however, that these findings may have been precipitated by the therapeutic crossover of lifestyle modification sessions into the metformin group per ethical necessity. Nevertheless, both lifestyle interventions and metformin therapy effectively reduced total T2DM incidence. Interestingly, lifestyle modifications were most protective in those aged 60 to 85 years at randomization; a nearly 50% reduction in overall T2DM incidence was found in this subgroup. Of note, lifestyle session attendance was positively correlated with age, with nearly double the participation among those age 60 or older at randomization. Thus, the effect of lifestyle interventions may have resulted from adherence rather than age as an independent determinant.

After 15 years post-randomization, the DPP groups were analyzed for diabetes development as well as microvascular complications.[17] By that time, the diabetes and microvascular outcomes were nearly convergent between the lifestyle and metformin groups,

although diabetes conversion was delayed for over 1 year in the lifestyle cohort (Figure 1). The convergence of cumulative T2DM may have resulted from waning lifestyle efforts or the introduction of lifestyle sessions into the remaining groups. However, a recent subgroup analysis of the metformin arm showed an enhanced protective effect among those with higher baseline fasting glucose (110-125 mg/dL) or HbA1c levels (6.0 – 6.4%) and women with past GDM.[18] Extra consideration for metformin therapy for the prevention of T2DM, therefore, should be afforded to these high-risk groups. Regarding microvascular complications, an inflection point was observed at a HbA1c of 6.2%, indicating the presence of hyperglycemia-mediated microvascular changes in prediabetics. Lifestyle modifications were especially protective against microvascular complications in women – a benefit not observed with metformin. These findings highlight the importance of early and aggressive intervention of prediabetes to avert or minimize the health and economic costs associated with vascular changes.

Several large RCTs have investigated the absolute efficacy of lifestyle interventions on diabetes prevention. The DaQing Diabetes Study compared the effects of dietary modification and increased physical activity versus controls in a large cohort with IGT.[19] Despite a gradual regression to baseline activity as well as caloric and macronutrient intakes by the end of a 6-year intervention period, significant reductions in T2DM incidence were observed in all lifestyle cohorts relative to controls (31-42% relative risk reduction and incidence rates 25-50% below that of the control group). A 20-year follow-up study demonstrated enduring and substantial reductions in diabetes incidence in the original lifestyle groups even when no significant differences in diet or activity were maintained at follow-up, although lifestyle adherence was

not assessed in the interim.[20] In fact, the pooled intervention groups had a 43% lower incidence of diabetes and those who did develop T2DM did so approximately 3.6 years later than controls. These durable effects of lifestyle modification echo analogous findings described in the DPP follow-up analyses. The DPPOS study showed a comparable median delay in diabetes onset of 4 years and 2 years with lifestyle modification and metformin therapy, respectively.[10] Moreover, a 23-year follow-up of the Da Qing study revealed a markedly lower cumulative all-cause and CVD mortality in the lifestyle groups compared to controls.[21] In another RCT concerning lifestyle interventions in those with IGT, Tuomilehto et al[22] similarly found a 58% lower cumulative incidence of diabetes with diet and exercise as compared to controls after over 3 years. Despite variable participation rates at 13 years post-randomization, incident T2DM was 43% lower in the lifestyle cohort.[23] Moreover, goal attainment scores regarding caloric and macronutrient goals, weight loss, and physical activity were strongly inversely correlated with diabetes development, with no cases of diabetes in those who attained at least 4 out of 5 lifestyle goals. These studies affirm the enduring impact of lifestyle changes in preventing or delaying T2DM, as well as suggest possible synergistic impacts of nutrition, physical activity, and weight loss. Setting defined lifestyle goals in these areas, therefore, may help address the various aspects of suboptimal glucose metabolism.

Weight loss appears to be a key determinant in reducing the progression of prediabetes to T2DM. In a large 2017 systematic review and meta-analysis of RCTs evaluating the long-term sustainability of various diabetes prevention strategies on T2DM incidence (aggregate n = 49,029), weight loss was the factor across all variables most strongly correlated with reduced conversion to diabetes.[24] Every kilogram lost was associated with an additional 7% relative risk

reduction. Moreover, an analysis of DPP study participants found a 16% relative risk reduction in diabetes incidence for every kilogram lost, further supporting weight loss as a key predictor of diabetes prevention.[25] The Tuomilehto study concluded similarly. Lifestyle interventions and metformin therapy may each produce clinically significant weight loss.[16] After 10 years, lifestyle interventions and metformin therapy were associated with a 2-kilogram and 2.5-kilogram weight loss, respectively, in the DPPOS study. While lifestyle interventions did result in more substantial weight loss after the first year of intervention, the weight was gradually regained; the metformin-associated weight loss, by contrast, was steadily maintained. Additionally, a meta-analysis of 31 RCTs (8,267 total patient-years) examining the metabolic effects of metformin on T2DM incidence demonstrated an average BMI decrease of 5.9% with approximately two years of metformin use.[26] These observations suggest that metformin may prove especially beneficial where patients are otherwise unable to achieve significant weight loss with lifestyle changes.

CONCLUSION

Prediabetes, especially in the setting of concomitant IFG and IGT, commonly converts to diabetes within years. Moreover, the condition is associated with microvascular changes and may represent an independent CVD risk factor, although further study in this area is warranted. There is strong evidence that lifestyle modification as well as metformin therapy, particularly when resulting in clinically significant weight loss, considerably reduces or delays the incidence of T2DM in those with prediabetes.

Evidence suggests that the preferred initial approach to diabetes prevention is goal-oriented multifactor lifestyle management due to its superior overall performance as well as complimentary CVD risk factor and long-term all-cause mortality risk reduction. Lifestyle modifications, even if incompletely maintained, may reduce the relative risk of diabetes for at least 20 years. Metformin alone provides slightly inferior benefits. Comparative outcomes suggest that metformin should be carefully considered to enhance lifestyle changes in particular clinical scenarios. These situations include: rising glycemic indices despite trial lifestyle management, inability to achieve clinically significant weight loss when appropriate, and in groups most likely to benefit from the medication (i.e. thoses with higher fasting glucose or HbA1c levels and women with a history of GDM). Considering this evidence, it is incumbent upon the provider to engage the patient in a dialogue about the risks of prediabetes and diabetes, to foster an honest and ongoing discussion regarding the attainment of lifestyle goals including weight loss, and to discuss the role of metformin when indicated.

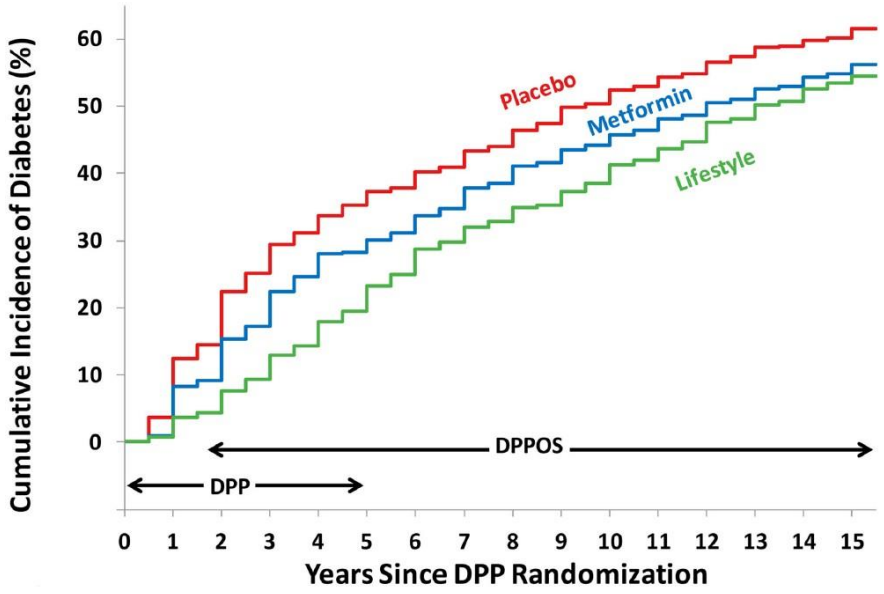

FIGURE 1.
Cumulative incidence of diabetes by treatment group among the 2776 DPPOS participants. The DPP and DPPOS periods, and the overlap between them, are indicated. Over the entire study, the incidence rates for participants were 7.0%, 5.7% and 5.2% per year for placebo, metformin and lifestyle, respectively, 27% and 18% lower for lifestyle and metformin vs. placebo, respectively ($p<0.0001$ and $p= 0.001$). The difference between lifestyle and metformin was not significant ($p=0.10$).

Excerpted from Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet*. Diabetes & Endocrinology [serial online]. November 2015;3(11):866-875.

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